**Functional interaction between the von-Hippel Lindau protein and Androgen receptor in ccRCC**

Antonella Falconieri[1], Chiara Boschelle[1], Giovanni Minervini[1], Silvio C.E. Tosatto[1,2], Maria Pennuto[1,3]

[1] Department of Biomedical Science, University of Padua, Padua, Italy

[2] CNR Institute of Neuroscience, Padua, Italy

[3] Veneto Institute of Molecular Medicine, Padua, Italy

**Introduction**
More than 80% of clear cell renal cell carcinoma (ccRCC) are linked to loss of function (LOF) mutations of the von Hippel-Lindau protein (pVHL). Males have a higher risk to develop renal cancer compared to females, implying a role for androgens in the etiology of the disease. The main mediator of androgen signaling is androgen receptor (AR). AR and pVHL have been reported to structurally and functionally interact with each other. However, how the functional relationship between AR and pVHL is regulated and how it impacts on ccRCC gender bias is unknown.
**Methods**
Here, we paired molecular, cellular and biochemical analysis to characterize pVHL/AR interaction in different ccRCC cell models.
**Results**
We found that AR interacts with both the full-length pVHL30 and the shorter pVHL19 isoform, and this interaction is subjected to androgen binding. By inhibiting protein synthesis and measuring the AR turnover, we show that pVHL expression influences AR stability in a isoform-specific manner. We confirmed that reintroduction of pVHL in RCC-pVHL- cells decreases cells proliferation, and activation of AR results in the recovery of cell proliferation. This finding suggests that AR in its active state may act as pro-proliferative factor in ccRCC.
**Discussion**
Taken together, our results indicate that both pVHL30 and pVHL19 interact with AR. Furthermore, the AR activity state has a key role in the regulation of AR/pVHL association, suggesting that the interplay among these proteins plays a role in determining ccRCC sex discrepancy.